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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/626,242	09/27/2000	Leo G. Frenken	PM-271592/T3	8145

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MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
PONNALURI, PADMASHRI	
ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 01/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/626,242	Frenken et al
Examiner	**Art Unit**
Padmashri Ponnaluri	1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 8, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above, claim(s) *5-9* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

NOTE: The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1639.

1. This application is 371 of PCT of application PCT/EP99/00481.

2. Claims 1-9 are currently pending in this application.

3. Applicant's election with traverse of Group I, claims 1-4, in Paper No. 13, filed on 11/8/02, is acknowledged. The traversal is on the ground(s) that Group II, claim 5 is drawn to a method of preparing a library according to claim 3 or 4 be examined with elected Group I claims. Applicants argue that in International Application PCT/EP99/00481, no lack of unity of invention was held, and the claims were examined together as one group. Applicants argue that the expression libraries of claims 1-4 are defined as the product of the method of preparing a library of claim , and the expression library and method of preparing them are linked by this technical feature forming a single inventive concept. Applicants further argue that the subject matter of claims 1-9 is considered as novel.

This is not found persuasive because the products of group I inventions can be prepared using several different methods; and as applicants pointed out that the special technical feature

is the product (library of repertoire encoding at least a part of variable domain of heavy chain derived from an immunoglobulin naturally devoid of light chains). However, the special technical feature is well known in the prior art (see Casterman et al) and thus the instant invention lacks unity.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 5-9 are withdrawn from further consideration pursuant to 37 CAR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13.

5. Claims 1-4 are currently being examined in this application.

6. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

7. This application does not contain an abstract of the disclosure as required by 37 CAR 1.72(b). An abstract on a separate sheet is required.

8. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CAR 1.78(a)(2) and (a)(5)).

9. Claim 4 is objected to under 37 CAR 1.75© as being in improper form because a multiple dependent claim 3. See MPEP § 608.01(n).

10.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite by reciting 'cloned from non-immunized source', clarification is requested what does applicants mean by non-immunized source.

Claim 1 recites '... each nucleic acid sequence encoding ....' which is vague and not clear whether applicants mean the nucleic acid sequence is from the repertoire of nucleic acid sequences. If applicants mean that 'each nucleic acid sequence' is from the repertoire of nucleic acid sequences, applicants are requested to amend the claim.

Claim 1 is indefinite by reciting ' at least part of a variable domain...'. Clarification is requested what does applicants mean by 'at least a part', does few amino acids is considered as at least a part or it has to be specific length or does it constitute any specific functional domains. Applicants are requested to amend the claim to clearly recite the part of variable domain of heavy chain.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-4 are rejected under 35 U.S.C. 102(a) as being anticipated by US Patent 5,800,988 (Casterman et al , filed on June 6, 1995).

The instant claims briefly recite an expression library comprising a repertoire of nucleic acid sequences, each nucleic acid sequence encoding a part of variable domain of a heavy chain derived from an immunoglobulin naturally devoid of light chains.

Casterman et al disclose immunoglobulins devoid of light chains (refers to 'naturally devoid of light chains' of the instant claims). The reference discloses that the disclosed immunoglobulins comprise two heavy polypeptide chains sufficient for formation of a complete antigen binding site (i.e., see column 2, lines 32-33). The reference discloses that the disclosed immunoglobulins are further characterized by the fact that they are the product of the expression in a prokaryotic or in a eukaryotic host cell of DNA or of cDNA having sequence of an immunoglobulin devoid of light chains as obtainable from lymphocytes or other cells of camelids (i.e., see column 2, lines 35-40) (refers to the instant claims 1-4). The reference discloses cDNA

libraries to isolate nucleic acid sequences coding for immunoglobulins of the invention (i.e., see column 11, lines 10-11). The reference discloses that the nucleic acid sequences of the disclosed immunoglobulins are used for the preparation of recombinant vectors and the expression of these sequences contained in the vectors by host cells (i.e., see column 11, lines 14-15). The reference discloses V_{HH} (variable heavy chain of immunoglobulin devoid of light chain) repertoire (refers to the repertoire of nucleic acid sequences of the instant claims) using DNA derived from an arbitrarily chosen tissue or cell type or V_{HH} repertoire using DNA obtained from B lymphocytes. The reference discloses in column 12, a cDNA library composed of nucleotide sequences coding for a heavy chain immunoglobulin by treating a sample containing lymphoid cells, especially from peripheral lymphocytes, spleen cells, lymph nodes or other lymphoid tissue from a healthy animal, especially selected from Camelids. The reference discloses that the preparation of the antibodies can also be performed without a previous immunization of Camelids (see column 14, lines 15-16) (refers to the 'non-immunized source' of the instant claims). Thus the reference clearly anticipates the claimed invention.

14. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 584421 A1, published March 02, 1994.

The instant claims briefly recite an expression library comprising a repertoire of nucleic acid sequences, each nucleic acid sequence encoding a part of variable domain of a heavy chain derived from an immunoglobulin naturally devoid of light chains.

EP 584421 A1 discloses immunoglobulins devoid of light chains. The immunoglobulins disclosed by the reference comprise two heavy chain polypeptide chains sufficient for the formation of a complete antigen binding site or several antigen binding site and devoid light polypeptide chains (refers to 'naturally devoid of light chains' of the instant claims) (i.e., see last paragraph in page 2). The reference discloses that the immunoglobulins can be isolated from animals, and are called 'heavy chain immunoglobulins. The reference discloses that the heavy chain immunoglobulins of the invention are secreted in blood of camelids (i.e., see page 3, lines 45). And the reference discloses methods for obtaining nucleotide sequences coding for all or part of the immunoglobulins, and the nucleotide sequences can be used for the preparation of recombinant vectors and the expression of these sequences contained in the vectors by host cells (refers to the instant claim 1) (i.e., see page 7). The reference discloses that V_H repertoire and libraries by cloning cDNA from lymphoid cells (i.e., see page 8). The reference discloses that in the method of obtaining cDNA library composed of nucleotide sequences encoding heavy-chain immunoglobulins, a sample containing lymphoid cells, especially peripheral, lymphocytes, spleen cells, lymph nodes or another lymphoid tissue from a healthy animal, especially selected among camelids (refers to cloned from a non-immunized source' of the instant claim) (i.e., see the example in page 8). Thus, the reference clearly anticipates the claimed invention).

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1-4 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Ghahroudi et al (FEBS Letters, 414 (1997) 521-526).

The instant claims briefly recite an expression library comprising a repertoire of nucleic acid sequences, each nucleic acid sequence encoding a part of variable domain of a heavy chain derived from an immunoglobulin naturally devoid of light chains.

NOTE that the instant claims are considered as the product-by-process claims, in which the limitation 'cloned from a non-immunized source' is considered as process limitation.

Ghahroudi et al disclose single domain antibody fragments from camel heavy-chain antibodies (refers to instant claims 1 and 3) . The reference discloses that the functional heavy chain immunoglobulins lacking light chain (refers to 'naturally devoid of light chains' of the instant claims) occur naturally in Camelidae. The reference discloses cloning repertoire of

variable domains of heavy chain antibodies (i.e., see the abstract). The reference discloses that V_{HH} library displayed on phage particles was generated by immunizing a camel. The reference discloses that libraries containing the variable region repertoire of heavy chains from immunized camel blood lymphocytes were constructed. The reference discloses mRNA isolation from the lymphocytes and cDNA synthesis and cloning the CDR3 sequence (refers to 'at least a part of variable domain of heavy chain' of the instant claims) (i.e., see the materials and methods section).

The claimed invention differs from the prior art teachings by reciting 'cloned from non-immunized source'. However, the claimed expression library comprising repertoire of nucleic acid sequences encoding at least a part of a variable domain of a heavy chain naturally devoid of light chains, appear to be the same or obvious variations of the reference libraries, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to determine and/or compare the specific method of making the libraries of the instant versus the reference method which would result in patentably distinct compounds. . In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed library is structurally and functionally different rom the library of the reference which uses a different method to synthesize the library. See in re Best 562F.2d 1252, 195 U. S. P. Q. 430 (CCPA 1977) and Ex parte Gray 10 USPQ2d 1922(PTO Bd.Pat. App. & Int. 1989).

"The instant claims are written as product-by-process claims. "Even though the product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability is based on the product itself. The patentability of a product does hot depend on its method of production. If the product in the product-by-process claims is same or as obvious from the product of the prior art, the claim is unpatentable Even though the prior art product was made by a different process." In re Thorpe, 777 F. 2d 695, 698, 227 U. S. P. Q. 964, 966 (Fed. Cir. 1985). (see MPEP 2113).

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 U. S. P. Q. 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 U. S. P. Q. 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 U. S. P. Q. 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 U. S. P. Q. 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CAR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CAR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CAR 3.73(b).

18. Claims 1-4 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,399,763. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims recite that the nucleic acid sequence encodes at least a part of a variable domain of a heavy chain, which would read on the reference recitation of heavy chain fragment comprising at least the three complementary determining regions and the parts of the frame work region that link them. The reference claim recitation enhancement of the library is considered as process limitations. Thus, the broadly recited instant claim would read on the reference expression library.

19. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to P. Ponnaluri whose telephone number is (703) 305-3884. The examiner is on ***Increased Flex Schedule*** and can normally be reached on Monday to Friday from 7.00 AM to 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

P. Ponnaluri
Patent Examiner
Technology Center 1600
Art Unit 1639
22 January 2003

PADMASHRI PONNALURI
PRIMARY EXAMINER

John J. Doll, Director
Technology Center 1600